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(54) Title: TREATMENT OF FIBROMYALGIA SYNDROME

(57) Abstract: A method for treating fibromyalgia syndrome with an agonist of α7 nicotinic acetylcholine receptors.

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AO

Treatment of Fibromyalgia Syndrome

Background

Fibromyalgia syndrome (FMS) is a complex chronic condition that causes widespread muscular pain and profound fatigue. Other symptoms include impaired memory, depression, impaired concentration, irritable bladder, sleep disturbance, and headaches. This debilitating, chronic affliction affects 10 million Americans and there is no known cure for the disease. Many of the current treatments have only a partial or temporary effects on some of the symptoms.

Tropisetron is an antagonist at the $5HT_3$ receptor that was developed as a treatment for emesis. In animal models, tropisetron, but not ondansetron, was shown to antagonize spatial navigation impairment in a complex spatial memory task (Pharm. Biochem. Behavior. *56*:571, 1997). The authors suggested, "the possible existence of other 5-HT_3 receptor subtypes might help to explain the different behavioral effects of ondansetron, tropisetron and itasetron." Recently, it has been reported that fibromyalgia patients treated with tropisetron showed a statistically significant reduction in their symptoms (Scand. J. Rheumatol. Suppl. 113:46-55, 2000). The positive effects of this drug in fibromyalgia patients were attributed to tropisetron's binding to the $5HT_3$ receptor.

Description of the invention

We have now discovered that tropisetron acts as a potent partial agonist of the α7 nicotinic acetylcholine receptor. This discovery links the symptoms of FMS to activity of α7 receptors rather than those of $5HT_3$ receptors.

The α7 nicotinic acetylcholine receptors are abundant in cholinergic brain areas important to cognition and memory. This receptor has also been associated with the modulation of neurotransmission and the modulation of long-term potentiation (LTP). This receptor may also function as a filter to gate external sensory inputs, thus making it an attractive target for treatment of cognitive deficits such as those observed in FMS patients. Many of the symptoms such as pain, memory loss, compromised attention, and irritable bladder exhibited by patients with FMS can be linked to activation or desensitization of the α7 receptor. We believe the etiology of FMS is linked to the α7 receptor and that patients with FMS would respond to treatment with α7 agonists, such as the compounds disclosed herein.

A variety of α7 agonists are known that are useful in all aspects of the present invention.

Accordingly, the present invention relates to the use of agonists of α7 nicotinic acetylcholine receptors to treat FMS. Therefore, in one aspect the present invention is directed to the treatment of FMS with α7 agonists. In a second aspect the invention is directed to the use of an α7 agonist to treat the symptoms of FMS. In another aspect the invention is directed to pharmaceutical compositions containing α7 agonists useful for the treatment or amelioration of FMS.

The invention relates to the use of an α7 agonist for the treatment or prophylaxis of fibromyalgia syndrome and fibromyalgia-related symptoms. The invention can be put into practice by clinical trials in which the alleviation of the symptoms in patients with FMS is measured in drug-treated and placebo controls.

In one aspect of the invention, the α7 agonist is a compound that has a K_i value of less than 1000 nM in the ^{125}I-α -Bungarotoxin binding to rat hippocampal membrane assay.

In another aspect of the invention, the α7 agonist is a compound that has an EC_{50} value of less than 30 μM in the functional rat oocyte assay.

In another aspect of the invention, the α7 agonist is a compound that has a K_i value of less than 1000 nM in the ^{125}I-α -Bungarotoxin binding to rat hippocampal membrane assay and an EC_{50} value in the functional rat oocyte assay of less than 30 μM.

Another aspect of the invention relates to a method for the manufacture of a medicament for the treatment or prophylaxis of fibromyalgia syndrome and fibromyalgia-related symptoms comprising an α7 agonist, wherein the α7 agonist is defined as described by any of the above embodiments.

We have discovered that the $5HT_3$ receptor antagonist tropisetron is a potent and selective partial agonist at the α7 receptor. In contrast, the structurally similar $5HT_3$ antagonist, ondansetron, was shown to lack activity at the α7 receptor.

Therefore, the memory effects of tropisetron are likely to arise from its action at the α7 receptor. Accordingly, we believe that the positive therapeutic activity of tropisetron in FMS patients is due to the action of this drug at the α7 receptor and not due to actions at the $5HT_3$ receptor as previously reported.

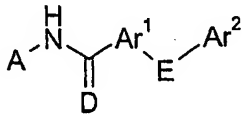
Brief description of the drawings:

Fig. 1 shows the currents elicited in frog oocytes expressing mouse nAChR α7-receptors by acetylcholine or tropisetron.

Detailed Description of the Invention:

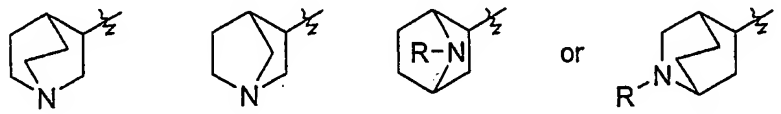
In a first embodiment of the invention a suitable α7 agonist is spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine-2'-one (Compound 1, Table 1). This compound is a selective α7 agonist with a wide safety margin. This compound is disclosed in U.S. Patent 5,902,814 the disclosure of which is incorporated herein in its entirety by reference. This compound is active in animal models of memory and cognition.

In a second aspect of the invention a suitable α7 agonist is a compound as disclosed in PCT publication WO 01/60821 the disclosure of which is incorporated herein in its entirety by reference, having the structure:



wherein:

A is selected from



II III IV or V

D is oxygen or sulfur;

E is a single bond, oxygen, sulfur, or NR^{10};

R is hydrogen or methyl;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 1 oxygen or sulfur atom;

Ar^2 is a 5- or 6-membered aromatic or heteroaromatic ring containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 2 oxygen or sulfur atom; or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 2 oxygen or sulfur atoms;

wherein if Ar^2 is unsubstituted phenyl, then Ar^1 is not pyrazolyl;

wherein the aromatic rings Ar^1 and Ar^2 are substituted with 0, 1, 2 or 3 substituents selected from halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4 and CF_3; but

if Ar^1 is phenyl and Ar^2 is quinolynyl, then Ar^2 is substituted with 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3 and CO_2R^4;

R^1, R^2, and R^3 are independently C_{1-4}alkyl, aryl, heteroaryl, $C(O)R^5$, $C(O)NHR^6$, $C(O)R^7$, SO_2R^8; or R^1 and R^2 may together be $(CH_2)_jG(CH_2)_k$ where G is oxygen, sulfur, NR^9, or a single bond;

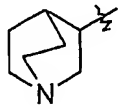
j is 2, 3 or 4;

k is 0, 1 or 2;

R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently C_{1-4}alkyl, aryl, or heteroaryl; or an enantiomer thereof and pharmaceutically acceptable salts thereof;

with the provisos that:

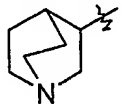
(1) if D represents oxygen, E represents a single bond, and A represents:



II

and either Ar^1 or Ar^2 represents a pyrazole ring , then all optional substituents on the pyrazole ring shall be hydrogen; and

(2) if Ar^1 represents a pyridine ring, Ar^2 represents an aryl ring, and A represents:



II

then all optional substituents on the pyridine ring shall be hydrogen.

Particular compounds that are embodiments of this aspect of the inventions are compounds below:

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);

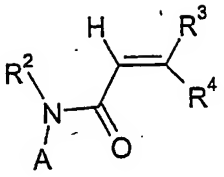
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide), compound 3, Table 1;

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);

N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);

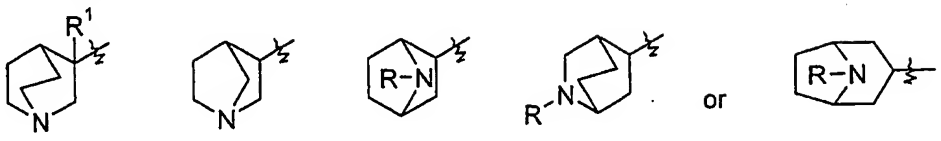
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide);
N-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*,*N*-dimethylamino)phenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide), or
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide)
or an enantiomer thereof, or a pharmaceutically-acceptable salt thereof.

In a third aspect of the invention a suitable α7 agonist is a compound as disclosed in PCT publication WO 01/29034 the disclosure of which is incorporated herein by reference in its entirety, having the structure:



wherein:

A represents a moiety selected from:



II III IV V or VI

R represents hydrogen or methyl;

R^1 and R^2 are independently hydrogen, or C_1–C_4 alkyl;

R^3 and R^4 are independently hydrogen, C_1–C_4 alkyl or SAr, provided that at least one of R^3 and R^4 is SAr;

Ar represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to four nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atom which may optionally be substituted with one or more substituents selected from: hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, $-CO_2R^5$, –CN, $-NO_2$, $-NR^6R^7$, $-CF_3$, $-OR^8$;

R^5, R^6, R^7, and R^8 are independently hydrogen, C_1–C_4 alkyl, aryl, heteroaryl, $-C(O)R^9$, $-C(O)NHR^{10}$, $-C(O)R^{11}$, $-SO_2R^{12}$; or,

R^6 and R^7 may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{13}, or, a bond;

j is 2 to 7;

k is 0 to 2;

R^9, R^{10}, R^{11}, R^{12}, and R^{13}, are independently C_1–C_4 alkyl, aryl, or heteroaryl;

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

Particular compounds that are embodiments of this aspect of the inventions are:

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)propenamide] hydrochloride;

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methylphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methylphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methylphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methylphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methoxyphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methoxyphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methoxyphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methoxyphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methoxyphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methoxyphenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-pyridylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-pyridylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyrimidinylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methyl-3-furanylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methyl-3-furanylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-imidazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)-3-(methyl)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzothiazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzothiazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(1-methyl-2-imidazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(1-methyl-2-imidazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-chlorophenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thienylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thienylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzoxazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzoxazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-trifluoromethyl-2-pyrimidinylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-fluorophenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-fluorophenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];

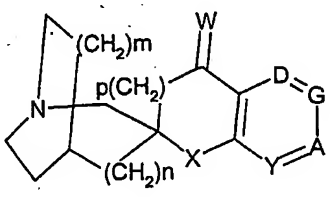
(R)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-fluorophenylthio)propenamide], or

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-fluorophenylthio)propenamide];

or an enantiomer thereof, or a pharmaceutically-acceptable salt thereof

In a fourth aspect of the invention a suitable α7 agonist is a compound as disclosed in U.S. Patent 6,110,914 the disclosure of which is incorporated herein by reference in its entirety, having the structure:



wherein n is 0 or 1;

m is 0 or 1;

p is 0 or 1;

X is oxygen or sulfur;

Y is CH, N or NO;

W is oxygen, H_2 or F_2;

A is N or $C(R^2)$;

G is N or $C(R^3)$;

D is N or $C(R^4)$;

with the proviso that no more than one of A, G, and D is nitrogen but at least one of Y, A, G, and D is nitrogen or NO;

R^1 is hydrogen or C_{1-4}alkyl;

R^2, R^3, and R^4 are independently hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OH, OC_{1-4}alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $-OSO_2CF_3$, or R^2 and R^3, or R^3 and R^4, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing 0, 1 or 2 nitrogen atoms, and substituted with one to two substituents independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OH, OC_{1-4}alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $-OSO_2CF_3$;

R^5 and R^6 are independently hydrogen, C_{1-4}alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;

j is 2 to 7;

k is 0 to 2;

R^7, R^8, R^9, R^{10}, and R^{11} are independently C_{1-4}alkyl, aryl, or heteroaryl,

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

Particular compounds that are embodiments of this aspect of the inventions are:

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine], Compound 2, Table 1;

5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)- furo[2,3-b]pyridine];

1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];

5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]; 5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];

spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline];

5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(1-azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carbonitrile];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carboxamide];
5'-N'-(3-chlorophenyl)aminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide];
spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile];
6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine], or
6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];
or an enantiomer, or a pharmaceutically-acceptable salt thereof.

Experimental:

We discovered that the $5HT_3$ receptor antagonist tropisetron is a potent and selective partial agonist at the α7 receptor (Figure 1). In contrast, the structurally similar $5HT_3$ antagonist, ondansetron, lacked activity at the α7 receptor (Table 1).

In earlier work (Pharm. Biochem. Behavior. *56*:571, 1997) tropisetron, but not ondansetron, antagonized spatial navigation impairment in a complex spatial memory task in animal models suggesting that behavioral differences were not due to actions at he $5HT_3$ receptor.

Test A - Assay for affinity at α7 nAChR subtype

^{125}I-α-Bungarotoxin (BTX) binding to rat hippocampal membranes.

Rat hippocampi were homogenized in 20 volumes of cold homogenisation buffer (HB): (in mM): tris(hydroxymethyl)aminomethane 50; $MgCl_2$ 1; NaCl 120; KCl 5: pH 7.4). The homogenate was centrifuged for 5 min at 1000 g, the supernatant was saved and the pellet re-extracted. The pooled supernatants were centrifuged for 20 min at 12000 g, washed, and re-suspended in HB. Membranes (30–80 μg) were incubated with 5 nM [^{125}I] α-BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM $CaCl_2$ or 0.5 mM EGTA [ethylene glycol-bis(β-aminoethylether)] for 2 h at 21 °C, and then filtered and washed four times over Whatman glass fiber filters (thickness C) using a Brandel cell harvester. Pre-treating the filters for 3 h with 1% (BSA/0.01% PEI (polyethyleneimine) in water was critical for low filter blanks (0.07% of total counts per minute). Non-specific binding was described by 100 μM (–)-nicotine, and specific binding was typically 75%.

Test B - Assay for affinity to the 5-HT_3 nAChR subtype

[^{3}H]zacopride binding. Binding of 0.5 nM [^{3}H]zacopride was assessed essentially as described in Test A using rat small-bowel muscularis membranes suspended in 50 mM Tris; 150 mM NaCl at pH 7.4. Incubation was continued for one hour.

Binding data analysis for Tests A and B

IC_{50} values and pseudo Hill coefficients (n_H) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding K_D values of 1.67 and 0.7 nM for the [^{125}I]-α -BTX and [^{3}H]zacopride ligands respectively. K_i values were estimated using the general Cheng-Prusoff equation (A):

$$K_i = [IC_{50}]/((2+([ligand]/K_D)^n)^{1/n}-1) \qquad (A)$$

where a value of n=1 was used whenever $n_H<1.5$ and a value of n=2 was used when $n_H \geq 1.5$. Samples were assayed in triplicate and were typically ± 5%. K_i values were determined using six or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 1 μM in Test A, indicating that they are expected to have useful therapeutic activity by interacting at the α7 receptor (Table 1).

Table 1. Binding Affinities

Compound	Stereo-chemistry	Binding Affinity (Ki/nM)	
		α_7	$5HT_3$
1	(R)	91	24000
2	(R)	14	NA
3	(R)	1.6	20000

Test C – Rat Oocyte Functional Assay

Xenopus oocytes Xenopus laevis frogs (Xenopus I, Kalamazoo, MI) were anesthetized using 0.15% tricaine. Oocytes were removed to OR2 solution: (in mM) 82 NaCl, 2.5 KCl, 5 HEPES, 1.5 NaH_2PO_4, 1 $MgCl_2$, 0.1 EDTA, pH 7.4. The oocytes were defolliculated by incubation in 25 mL OR_2 containing 0.2% collagenase 1A (SIGMA) two times for 60 min on a platform vibrating at 1 Hz and stored in Leibovitz's L-15 medium. Oocytes were injected the following day. Leibovitz's L-15 medium contained 50 µg/mL gentomycin, 10 units/mL penicillin, and 10 µg/mL streptomycin.

Preparation and injection of cRNA Rat nAChR α7 was cloned in-house (Luhowskyj). Non-polyadenylated cRNA was prepared from cDNA using mMessage mMachine SP6 (Ambion) according to the manufacturer's instructions.

Recording The external recording solution consisted of (in mM) 90 NaCl, 1 KCl, 1 $MgCl_2$, 1 $BaCl_2$, 5 HEPES, pH 7.4. Two-electrode voltage-clamp recording was carried out using an Oocyte Clamp amplifier (model OC 725C ,Warner Inst., Hamden, CT). Oocytes were impaled with two electrodes of 1-2 MΩ tip resistance when filled with 3M KCl. Recordings were begun when membrane potential became stable at potentials negative to –20 mV. Membrane potential was clamped at –80 mV unless otherwise noted. ACh, (-) was purchased from SIGMA.

Calculation of current amplitude and curve fitting Current amplitude was measured from baseline to peak. EC_{50}'s, maximal effect, and Hill slopes were estimated by fitting the data to the logistic equation using GraphPad Prism (GraphPad Software, Inc. San Diego, CA)

Figure 1 shows the effect of acetylcholine and tropisetron on oocytes expressing mouse nAChR α7. In the upper panel, representative traces of current elicited in oocytes expressing mouse nAChR α7 are illustrated. Traces shown are from the same oocyte; superfusion of acetylcholine and tropisetron begins at arrow (5 min between agonist

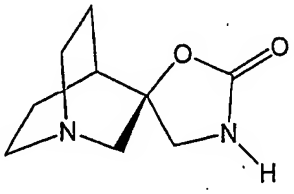
applications). In the lower panel, concentration-response curve to acetylcholine and tropisetron are shown. Data are fit by the logistic equation.

We claim:

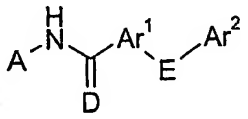
1. A method comprising the use of an α7 agonist for the treatment or prophylaxis of fibromyalgia syndrome and fibromyalgia-related symptoms.

2. The method according to Claim 1 wherein the α7 agonist is a compound that has a K_i value of less than 1000 nM in the ^{125}I-α-Bungarotoxin binding to rat hippocampal membrane assay.

3. The method according to Claim 1 wherein said α7 agonist is a compound having the structure

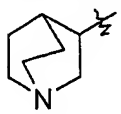


4. The method according to Claim 1, wherein the α7 agonist is a compound having the structure:



wherein:

A is selected from



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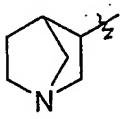

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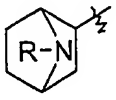
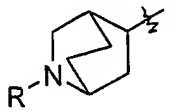


IV

or



V

D is oxygen or sulfur;

E is a single bond, oxygen, sulfur, or NR^{10};

R is hydrogen or methyl;

Ar^1 is a 5- or 6-membered aromatic or heteroaromatic ring containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 1 oxygen or sulfur atom;

Ar^2 is a 5- or 6-membered aromatic or heteroaromatic ring containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 2 oxygen or sulfur atom; or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing 0, 1, 2 or 3 nitrogen, oxygen or sulfur atoms, wherein there is no more than 2 oxygen or sulfur atoms;

wherein if Ar^2 is unsubstituted phenyl, then Ar^1 is not pyrazolyl;

wherein the aromatic rings Ar^1 and Ar^2 are substituted with 0, 1, 2 or 3 substituents selected from halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3, CO_2R^4 and CF_3; but

if Ar^1 is phenyl and Ar^2 is quinolynyl, then Ar^2 is substituted with 0, 1, 2 or 3 substituents selected from C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, CN, NO_2, NR^1R^2, $CH_2NR^1R^2$, OR^3, CH_2OR^3 and CO_2R^4;

R^1, R^2, and R^3 are independently C_{1-4}alkyl, aryl, heteroaryl, $C(O)R^5$, $C(O)NHR^6$, $C(O)R^7$, SO_2R^8; or R^1 and R^2 may together be $(CH_2)_jG(CH_2)_k$ where G is oxygen, sulfur, NR^9, or a single bond;

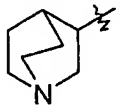
j is 2, 3 or 4;

k is 0, 1 or 2;

R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are independently C_{1-4}alkyl, aryl, or heteroaryl; or an enantiomer thereof and pharmaceutically acceptable salts thereof;

with the provisos that:

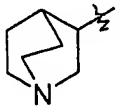
(1) if D represents oxygen, E represents a single bond, and A represents:



II

and either Ar^1 or Ar^2 represents a pyrazole ring , then all optional substituents on the pyrazole ring shall be hydrogen; and

(2) if Ar^1 represents a pyridine ring, Ar^2 represents an aryl ring, and A represents:



II

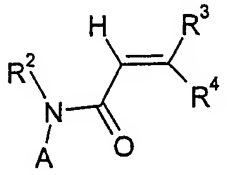
then all optional substituents on the pyridine ring shall be hydrogen.

5. The method according to Claim 4, wherein said compound is selected from:

N-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide);

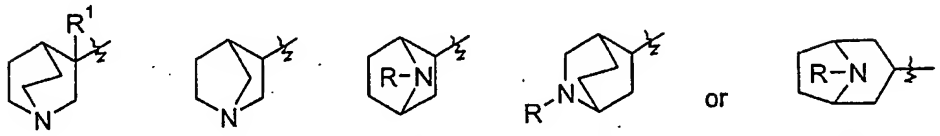
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide);
N-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ;
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide);
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide), or
N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide)
or an enantiomer thereof, or a pharmaceutically-acceptable salt thereof.

6. The method according to Claim 1, wherein the α7 agonist is a compound having the structure:



wherein:

A represents a moiety selected from:



II III IV V or VI

R represents hydrogen or methyl;

R^1 and R^2 are independently hydrogen, or C_1–C_4 alkyl;

R^3 and R^4 are independently hydrogen, C_1–C_4 alkyl or SAr, provided that at least one of R^3 and R^4 is SAr;

Ar represents a 5- or 6-membered aromatic or heteroaromatic ring containing zero to three nitrogen atoms, zero or one oxygen atom, and zero or one sulfur atom or an 8-, 9- or 10-membered fused aromatic or heteroaromatic ring system containing zero to four nitrogen atoms, zero to one oxygen atom, and zero to one sulfur atom which may optionally be substituted with one or more substituents selected from: hydrogen, halogen, C_1–C_4 alkyl, C_2–C_4 alkenyl, C_2–C_4 alkynyl, aryl, heteroaryl, $-CO_2R^5$, –CN, $-NO_2$, $-NR^6R^7$, $-CF_3$, $-OR^8$;

R^5, R^6, R^7, and R^8 are independently hydrogen, C_1–C_4 alkyl, aryl, heteroaryl, $-C(O)R^9$, $-C(O)NHR^{10}$, $-C(O)R^{11}$, $-SO_2R^{12}$; or,

R^6 and R^7 may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{13}, or, a bond;

j is 2 to 7;

k is 0 to 2;

R^9, R^{10}, R^{11}, R^{12}, and R^{13}, are independently C_1–C_4 alkyl, aryl, or heteroaryl;

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

7. The method according to Claim 6, wherein said compound is selected from:

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)propenamide] hydrochloride;

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methylphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-methoxyphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-methoxyphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-methoxyphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-methoxyphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methoxyphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methoxyphenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyridylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyridylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-pyridylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-pyridylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-pyrimidinylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-pyrimidinylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-methyl-3-furanylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-methyl-3-furanylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-imidazolylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(phenylthio)-3-(methyl)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzothiazolylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzothiazolylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(1-methyl-2-imidazolylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(1-methyl-2-imidazolylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propenamide];

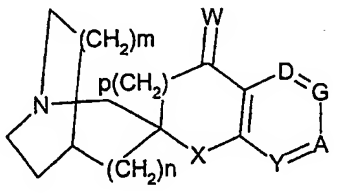
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-chlorophenylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thienylthio)propenamide];

N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thienylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-benzoxazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-benzoxazolylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-trifluoromethyl-2-pyrimidinylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(4-fluorophenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(4-fluorophenylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
(R)-N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(2-thiazolo[4,5-b]pyridylthio)propenamide];
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[Z-3-(3-fluorophenylthio)propenamide], or
N-(1-aza-bicyclo[2.2.2]oct-3-yl)[E-3-(3-fluorophenylthio)propenamide];
or an enantiomer thereof, or a pharmaceutically-acceptable salt thereof

8. The method according to Claim 1, wherein the α7 agonist is a compound having the structure:



wherein n is 0 or 1;
m is 0 or 1;
p is 0 or 1;
X is oxygen or sulfur;
Y is CH, N or NO;
W is oxygen, H_2 or F_2;
A is N or C(R^2);
G is N or C(R^3);
D is N or C(R^4);
with the proviso that no more than one of A, G, and D is nitrogen but at least one of Y, A, G, and D is nitrogen or NO;
R^1 is hydrogen or C_{1-4}alkyl;
R^2, R^3, and R^4 are independently hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OH, OC_{1-4}alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $-OSO_2CF_3$, or R^2 and R^3, or R^3 and R^4, respectively, may together form another six

membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing 0, 1 or 2 nitrogen atoms, and substituted with one to two substituents independently selected from hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, aryl, heteroaryl, OH, OC_{1-4}alkyl, CO_2R^1, –CN, $–NO_2$, $–NR^5R^6$, $–CF_3$, $-OSO_2CF_3$;

R^5 and R^6 are independently hydrogen, C_{1-4}alkyl, $C(O)R^7$, $C(O)NHR^8$, $C(O)OR^9$, SO_2R^{10} or may together be $(CH_2)_jQ(CH_2)_k$ where Q is O, S, NR^{11}, or a bond;

j is 2 to 7;

k is 0 to 2;

R^7, R^8, R^9, R^{10}, and R^{11} are independently C_{1-4}alkyl, aryl, or heteroaryl,

or an enantiomer thereof, and the pharmaceutically acceptable salts thereof.

9. The method according to Claim 8, wherein said compound is selected from:
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)- furo[2,3-b]pyridine];
1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];
5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine]; 5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline];
5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];

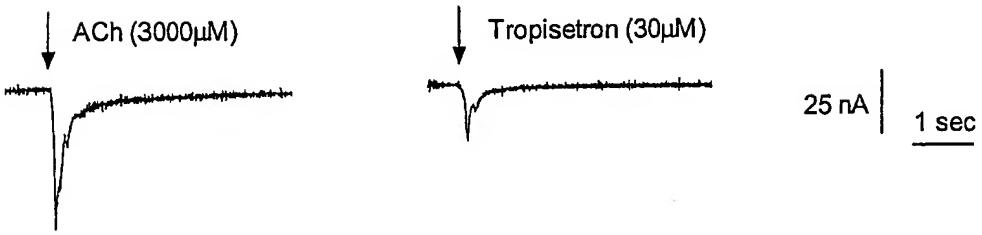
5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(1-azetidinyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carbonitrile];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5'carboxamide];
5'-N'-(3-chlorophenyl)aminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine];
4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine];
spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide];
spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile];
6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine], or
6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine];
or an enantiomer, or a pharmaceutically-acceptable salt thereof.

10. The use of an α7 antagonist for the manufacture of a medicament for the treatment or prophylaxis of fibromyalgia syndrome and fibromyalgia-related symptoms comprising an α7 agonist.

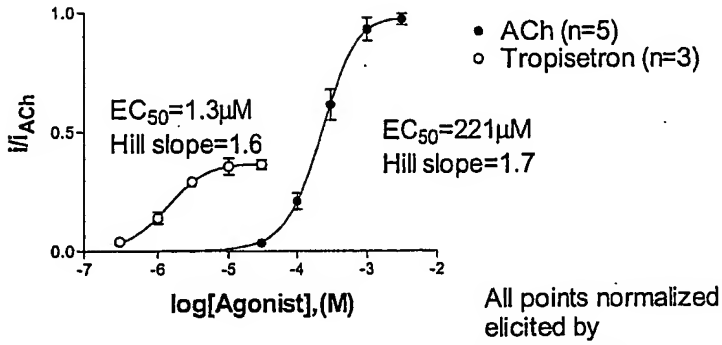
11. The use according to Claim 10, wherein the α7 agonist is a compound that has a K_i value of less than 1000 nM in the ^{125}I-α-Bungarotoxin binding to rat hippocampal membrane assay.

12. The use of an α7 antagonist for the manufacture of a medicament comprising an α7 agonist compound having a structure according to any one of Claims 3, 4, 5, 6, 7, 8 or 9.

Tropisetron (ICS-205,930) is a nAChR α7 Agonist



Traces show current elicited by superfusion (at arrow) of ACh and Tropisetron in the same oocyte expressing mouse nAChR α7 (5 minutes between agonist applications).



All points normalized to current elicited by 3000μM Ach

Fig. 1

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(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

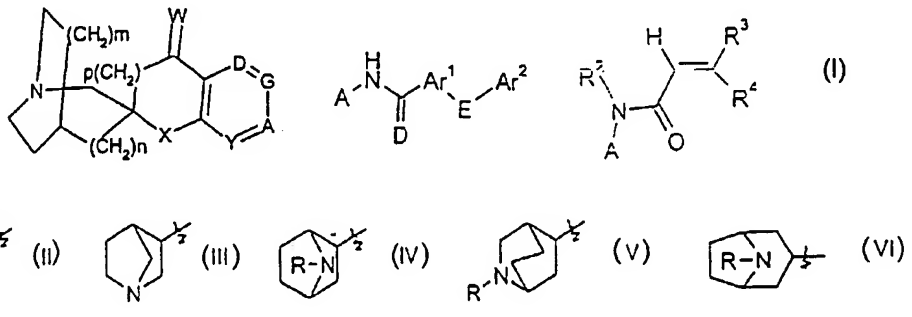
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

(88) Date of publication of the international search report:
13 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AZABICYCLIC COMPOUNDS FOR THE TREATMENT OF FIBROMYALGIA SYNDROME



(57) Abstract: A method for treating fibromyalgia syndrome with an agonist of α7 nicotinic acetylcholine receptors.

WO 03/032897 A3

INTERNATIONAL SEARCH REPORT

national application No.
PCT/SE 02/01887

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 453/02, 498/20, 451/04, 453/06, A61K 31/435, 31/40, 31/46, 31/44, A61P 25/00, 21/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN-CAPLUD, MEDLINE, EMBASE, WPI, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0216358 A2 (PHARMACIA & UPJOHN COMPANY), 28 February 2002 (28.02.02), formula I --	1-2,4-5, 10-12
P,X	WO 0216357 A2 (PHARMACIA & UPJOHN COMPANY), 28 February 2002 (28.02.02), formula I --	1-2,4-5, 10-12
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X	WO 0160821 A1 (ASTRAZENECA AB), 23 August 2001 (23.08.01), formula I --	1-2,4-5, 10-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 March 2003	25 -03- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer FERNANDO FARIETA/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

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International application No.
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X	Scand J Rheumatol, Vol. 29, Suppl. 113, 2000, K. Höcherl et al: "Effect of tropisetron on circulating catecholamines and other putative biochemical markers in serum of patients with fibromyalgia", page 46 - page 48	
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A	WO 9606098 A1 (ASTRAAKTIEBOLAG), 29 February 1996 (29.02.96)	1,8-12
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X	WO 9956745 A1 (ASTRA AKTIEBOLAG), 11 November 1999 (11.11.99), claims 1-28	1-2,3,8-12
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A	J. Med. Chem., Vol. 43, 2000, George Mullen et al: "(-)-Spiro(1-azabicyclo(2.2.2)octane-3,5'-oxazolidin -2'-one), a Conformationally Restricted Analogue of Acetylcholine, Is a Highly Selective Full Agonist at the alpha7 Nicotinic Acetylcholine Receptor", page 4045 - page 4050, Scheme 1	1-3,8-12
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01887

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0190920 A2 (A.H. ROBINS COMPANY, INCORPORATED), 13 August 1986 (13.08.86), formula I ---	1,4-5,10-12
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A	US 5990162 A (MARTIN B. SCHARF), 23 November 1999 (23.11.99), formula I ---	1,4-5,10-12
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01887

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-9
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☒ Claims Nos.: 1-2,10-11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
see next sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

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Box I.1

Claims 1-9 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for this claims. The search has been based on the alleged effects of the compounds.

Box I.2

The claims contain a plurality of different compounds and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT such an extent that a meaningful search of the whole scope of the claims is impossible.

Expressions such as "alpha-7 agonist" or "Ki value of less than" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Consequently, the search has mainly been carried out for those parts which appear to be clear, supported and disclosed, namely claims 3-9.

.../...

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Box II

According to Article 34 (3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features that define a contribution which each of the inventions makes over the prior art.

A search for this special technical feature among the claims of the present application did not reveal such unifying, novel technical feature.

Accordingly, the following inventions were found:

I. Claims 3, 8-9, and partly 1-2 and 10-12
II. Claims 4-5, and partly 1 and 10-12
III. Claims 6-7, and partly 1 and 10-12

The special technical feature of the claims is azabicyclic compounds. Such compounds are known in the prior art, see for example WO 96/06098 A1. Since there is no unifying novel technical feature, the claims are divided into three different inventions.

The search has been limited to invention I, II and III.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01887

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